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Abstract: OBJECTIVE The aim of this systematic review was to assess evidence on dental adverse effects associated with chemotherapy (CH) administered to children with cancer. MATERIAL AND METHODS Eight databases were searched without restrictions up to March 2017 for studies reporting on dental effects of CH administered for childhood cancer. After elimination of duplicates, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of Relative Risks (RR) and Mean Differences (MD) and their 95% Confidence Intervals (CI) were performed, followed by meta-regression and sensitivity analyses. RESULTS The literature search identified a total of 15 non-randomized case-control studies including at least 2315 patients (mean age at diagnosis or CH of 6.6 years; 36% male) followed for up to 22.9 years after CH. Meta-analysis indicated that CH was associated with increased risk for tooth agenesis compared to healthy controls (RR = 2.47; 95% CI = 1.30-4.71; P = 0.006). This translated to every seventh child with CH having agenesis of at least one tooth that would not otherwise have. Additionally, CH was significantly associated with increased risk of tooth discoloration, arrested tooth development, enamel hypoplasia, microdontia, premature apexification, and decreased salivary flow rate, as well as worse oral hygiene and greater caries experience compared to controls. However, the strength of evidence was very low due to the inclusion of non-randomized study designs with high risk of bias. CONCLUSIONS Current evidence from childhood cancer survivors indicates that chemotherapy is associated with considerable dental adverse effects that might be associated with greater burden of disease and treatment costs.

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Adverse effects of chemotherapy on the teeth and surrounding tissues of children with cancer: a systematic review with meta-analysis

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Abstract

Objective: The aim of this systematic review was to assess evidence on dental adverse effects associated with chemotherapy (CH) administered to children with cancer.

Material and methods: Eight databases were searched without restrictions up to March 2017 for studies reporting on dental effects of CH administered for childhood cancer. After elimination of duplicates, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of Relative Risks (RR) and Mean Differences (MD) and their 95% Confidence Intervals (CI) were performed, followed by meta-regression and sensitivity analyses.

Results: The literature search identified a total of 15 non-randomized case-control studies including at least 2315 patients (mean age at diagnosis or CH of 6.6 years; 36% male) followed for up to 22.9 years after CH. Meta-analysis indicated that CH was associated with increased risk for tooth agenesis compared to healthy controls (RR=2.47; 95% CI=1.30 to 4.71; P=0.006). This translated to every seventh child with CH having agenesis of at least one tooth that would not otherwise have. Additionally, CH was significantly associated with increased risk of tooth discoloration, arrested tooth development, enamel hypoplasia, microdontia, premature apexification, and decreased salivary flow rate, as well as worse oral hygiene and greater caries experience compared to controls. However, the strength of evidence was very low due to the inclusion of non-randomized study designs with high risk of bias.

Conclusions: Current evidence from childhood cancer survivors indicates that chemotherapy is associated with considerable dental adverse effects that might be associated with greater burden of disease and treatment costs.

KEYWORDS

childhood cancer; chemotherapy; adverse effects; teeth; tooth agenesis; caries; meta-analysis

MAIN TEXT

INTRODUCTION

Rationale

Considerable improvements have been seen during the last decades in the development of effective treatment protocols for childhood cancer, which usually consist of multiagent chemotherapy (CH), radiotherapy, or a combination of both. For example, the cure rate for Acute Lymphoblastic Leukemia (ALL), which is the most common childhood malignancy [1], has increased from less than 30% during the 1960s to an 80% to 86% 5-year overall survival [2].

Although developments in the curative therapy of childhood cancer have led to dramatic improvements in survival, mortality rates of childhood cancer survivors continue to be elevated for many years beyond 5-year survival compared to the general population [3]. Furthermore, childhood cancer survival is associated with many treatment-related late sequelae with potential effect on physical function including among others neurocognitive dysfunction, cardiopulmonary toxicity, endocrinopathy, and secondary malignancy, the frequency and severity of which depends on sex, age at diagnosis, and cumulative dose-exposures of specific treatment modalities [4-6]. Childhood cancer survivors are also prone to psychological distress that is associated with academic underachievement, underemployment, and functional limitations, which may adversely affect health status [7,8].

Likewise, several studies have assessed the potential impact of childhood cancer and its treatment on oral health status. As such, high prevalence of oral manifestations has been reported among pediatric cancer patients receiving CH that included among others gingivitis [9,10], caries [9-13], mucositis [10,13,14], cheilitis [10], oral pain [14], periodontitis [10], recurrent herpes [10], altered salivary immunological conditions [12,13], xerostomia [13,14], and disturbances in the number or development of teeth [9,11,12]. These adverse effects might have considerable impact on the functional or psychological status of childhood cancer survivors and ultimately their quality of life, while they may be associated with considerable financial burden. Therefore, the adoption of measures for the prevention or treatment of oral health related complications of childhood cancer treatment might be appropriate.

The current evidence base for any adverse effects of cancer treatment on the teeth of children is rather bleak. Only a single systematic review exists on this subject [15] that has several issues like being

outdated, involving questionable a priori design, limited search, inadequate assessment of the included studies risk of bias, and no quantitative synthesis. Additionally, assessed interventions included radiotherapy, CH, and hematopoietic cell transplant treatment, even though evidence for both independent and additive effects of each treatment was found [15]. This makes accurate estimations about the contribution of each therapeutical approach to the development of adverse effects difficult and therefore has limited value from a preventive or therapeutic side.

Aim

Current evidence on short- or long-term dental complications of CH administered to children with cancer is limited. Therefore, aim of the present systematic review was to assess in an evidence-based manner the existing data from clinical studies on humans and try to answer the question: *What are the adverse effects on the dentition and surrounding tissues of CH administered to children with cancer*?

MATERIAL AND METHODS

Protocol and registration

The review's protocol was made a priori following the PRISMA-P statement [16], registered in PROSPERO (CRD42017058660), and all post hoc changes were appropriately noted. This systematic review was conducted and reported according to Cochrane Handbook [17] and PRISMA statement [18], respectively.

Eligibility criteria

According to the Participants Intervention Comparison Outcome Study design schema (PICOS), we included both randomized and non-randomized clinical studies on human children up to 18 years of age, sex, or ethnicity with any kind of cancer being treated with CH. The primary outcome of this systematic review was tooth agenesis, while the secondary outcomes included developmental defects of teeth, clinical inflammatory or caries indices, and salivary outcomes. Excluded were non-clinical studies, case reports, animal studies, and all studies where CH is combined with radiotherapy.

Information sources and literature search

Eight electronic databases (MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts of Reviews of Effects, Virtual Health Library, Scopus, Web of Science, and ClinicalTrials.gov) were systematically searched by one author (SNP) without any limitations from inception up to March, 2017 (Appendix 1). Additionally, five sources (Google Scholar, International Standard Registered Clinical/ soCial sTudy Number Registry, Directory of Open Access Journals, Digital Dissertations, and metaRegister of Controlled Trials) and the reference/citation lists of included trials were manually searched for any additional trials. No limitations concerning publication language, publication year, or publication status were applied.

Study selection

The eligibility of identified studies was checked sequentially from their title, abstract, and full-text against the eligibility criteria by one person (DMB) and were subsequently checked independently by a second one (SNP), with any conflicts being resolved by a third person (TE).

Data collection and data items

Study characteristics and numerical data were extracted from included studies independently by two authors (DMB, SNP) using predefined and piloted extraction forms including: (i) study characteristics (design, clinical setting, country), (ii) patient characteristics (number, sex, age), (iii) cancer type, (iv) CH type, (v) follow-up after CH, and (vi) outcomes assessed. Piloting of the forms was performed during the protocol stage until over 90% agreement was reached. Missing or unclear information was calculated, whenever possible.

Risk of bias in individual trials

The risk of bias of included randomized trials was to be assessed using Cochrane's risk of bias tool [17]. The risk of bias of included non-randomized studies (NRS) was assessed using the Newcastle-Ottawa scale for case-control studies [19].

Outcomes and data synthesis

The primary and secondary outcomes of this review were either binary or continuous and were expressed as Relative Risks (RR) or Mean Differences (MD), respectively with their corresponding 95% Confidence Intervals (CI). Statistically significant results were translated to their Numbers Needed to Treat (NNT) to gauge their clinical relevance.

As adverse effects of CH are bound to be affected by the patient's age, dental/skeletal growth phase, cancer type, CH type or duration, and the patient's immunologic response, a wide variation of true effects was expected and a random-effects model was judged a priori sensible, based on biological, clinical, and statistical grounds [20]. The alternative Paule-Mandel random-effects estimator was used instead of the more widely known DerSimonian and Laird [21] one, based on contemporary guidelines, due to its improved performance [22].

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and calculating the tau^2 and the I^2, respectively; I^2 defines the proportion of total variability in the result explained by heterogeneity, and not by chance [23]. Heterogeneity was roughly categorized as low moderate, and high according to I^2 values of 25%, 50%, and 75% [23], although the heterogeneity's localization on the forest plot was also examined. Additionally, the 95% CIs around tau^2 and I^2 were calculated [24] to quantify our uncertainty around these estimates. 95% predictive intervals were calculated for meta-analyses of ≥3 trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting [25]. All analyses were conducted in Stata SE version 14.2 (StataCorp LP, College Station, Texas, USA) by one author (SNP) and the dataset was made freely available [26]. A two side $P \leq 0.05$ was considered significant for hypothesis-testing, except for $P \leq 0.10$ used for tests of between-studies or between-subgroups heterogeneity [27].

Additional analyses and quality of meta-evidence

Possible sources of heterogeneity were *a priori* planned to be sought through mixed-effects subgroup analyses and random-effects meta-regression for meta-analyses of ≥ five studies according to (i) patient characteristics (age, sex, ethnicity, cancer type, phase of dentition, oral health) (ii) preventive or therapeutic interventions administered prior to or during CH, and (iii) CH-related characteristics, but could not be ultimately conducted.

Robustness of the results was planned *a priori* to be checked with sensitivity analyses based on (i) inclusion/exclusion of trials with methodological shortcomings, (ii) improvement of the GRADE classification, and (iii) inclusion/exclusion of large-scale studies (judged arbitrarily as having at least 100 patients).

The overall quality of meta-evidence (i.e. the strength of clinical recommendations) was rated using the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, as very low, low, moderate, or high [28] and Summary of Findings tables were constructed using the improved format proposed by Carrasco-Labra et al. [29]. The minimal clinical important [30], large, and very large effects were defined as half, one, and two standard deviations (using the average standard deviation for an outcome across included studies), respectively. Arbitrary cut-offs of 1.5, 2.0, and 5.0 [31] were adopted for RR. The produced forest plots were augmented with contours denoting the magnitude of the observed effects [32] to assess heterogeneity, clinical relevance, and imprecision.

RESULTS

Study selection

The literature search yielded a total of 741 hits (Fig. 1), 92 of which proceeded to full text assessment after eliminating duplicates and ineligible studies by title or abstract (Appendix 2). Finally, a total of 16 papers were identified as eligible for inclusion in the present systematic review. After pooling multiple papers relating to the same study, a total of 15 unique clinical studies published in English between 1987 and 2016 were included.

Study characteristics

The descriptive characteristics of the 15 included studies can be seen in Table 1a and Table 1b [12,13,33-46]. From these, none was a randomized clinical trial and all were retrospective non-randomized studies. Most studies were conducted in university clinics (n=12; 80%) in 12 different countries. Overall, at least 2315 patients were included (from the 15 studies reporting patient sample) with a mean age of diagnosis or CH 6.6 years (from the 8 studies reporting this age) and with 36% of the patients being male (from the 12 studies reporting even partly patient sex). These patients had been treated with various types of CH and

re-examined either during CH (3 studies) or after an average follow-up period ranging from 1.4 to 22.9 years post CH (from the 9 studies reporting mean follow-up). The primary outcome of tooth agenesis was the most popular (assessed in the same way from 5 studies), followed by the secondary outcomes of microdontia, premature apexification, caries experience (through the Decayed-Missing-Filled-Teeth [DMFT] index), plaque/gingival indices, enamel hypoplasia, arrested root development, tooth discoloration, salivary buffer capacity or flow rate, and Streptococcus mutans counts.

Risk of bias within studies

The methodological adequacy (with possible effects on its bias risk) of identified studies with the Newcastle-Ottawa tool is given in detail in Appendix 3 and summarized in Table 2. The selection of cases/controls was found to be good in 5 (33%) of the studies, very good in 7 (47%) of the studies, and perfect in 3 (20%) of the studies. The comparability of cases and controls was poor in 5 (33%) of the studies, partial in 3 (20%) of the studies, and perfect in 7 (47%) of the studies. Finally, the domain of exposure was limited in 10 (67%) of the studies, partially adequate in 4 (27%) of the studies, and adequate in one (7%) of the studies. This latter study [46] was the single study that completely fulfilled all three domains, while the remaining 14 studies had at least one limitation in a domain.

Results of individual studies and data synthesis

The results of the primary and secondary outcomes from each included study can be found in the provided dataset [26], while the re-analysis of raw data provided in tabular form by a single study [35] is given in Appendix 4. As far as data synthesis of the primary outcome is concerned, CH was associated with a considerable increase in the risk of tooth agenesis compared to untreated patients (5 studies; RR=2.47; 95% CI=1.30 to 4.71; P=0.006; Table 3; Fig. 2). Moderate to considerable heterogeneity was seen, but estimates were highly imprecise for both absolute heterogeneity (tau^2=0.31; 95% CI=0 to 5.03) and relative heterogeneity (I^2=61%; 0% to 96%), which resulted in a very wide random-effects prediction for prospective CH patients with RRs ranging from 0.32 to 19.40. The average effect of CH on tooth agenesis was translated to an NNT of 7, which means that every 7^{th} child with cancer exposed to CH may develop tooth agenesis that he or she would not have otherwise (Table 4).

As far as the secondary outcomes are concerned, CH was associated with statistically significant ($P<0.05$) increases in the risk of microdontia (4 studies; RR=12.41; Fig. 3), enamel hypoplasia (2 studies; RR=3.08), arrested tooth development (2 studies; RR=2.75), premature apexification (3 studies; RR=4.53; Fig. 4), and tooth discoloration (2 studies; RR=3.25). Additionally, CH was associated with statistically significant ($P<0.05$) increases in the average plaque index (3 studies; MD=0.60 units), gingival index (3 studies; MD=0.38 units), DMFT index (3 studies; MD=3.07 teeth), and DT index (2 studies; MD= 3.55 teeth), as well as with significant decreases in the MT index (2 studies; MD=-0.56 teeth) and salivary flow rate (2 studies; MD= -0.19 ml/min). As far as the magnitude of observed effects is concerned (Table 4), the greatest increase in the risks of adverse effects was seen for tooth discoloration (where every 2nd child with CH would be affected), arrested root development (where every 4th child with CH would be affected), and enamel hypoplasia (where every 8th child with CH would be affected).

Finally, the GRADE approach was used to assess the quality of meta-evidence for the primary and secondary outcomes (Table 5a and 5b). As all analyses were based on non-randomized studies with high risk of bias due to methodological shortcomings, the confidence in the estimates is very low according to the GRADE approach for all outcomes. Large effect magnitudes were seen for some outcomes with NNTs<10 (Table 4), but no upgrade was done, due to existing methodological limitations.

Additional analyses

Several subgroup and sensitivity analyses were planned in the review's protocol, but could not be eventually performed as only one meta-analysis included at least 5 studies and their reporting of patient or treatment details was suboptimal. Only meta-regressions of tooth agenesis with patient age, patient sex, and follow-up duration could be conducted (Appendix 5), which did not find any significant modifying effect.

Likewise, two planned sensitivity analyses could not be conducted, as no randomized and no prospective non-randomized studies were ultimately identified. A sensitivity analysis according to sample size of the included studies (Appendix 6) indicated that the results were robust enough.

DISCUSSION

Summary of evidence

To our knowledge this is the first study to summarize and assess in a systematic manner the adverse effects on the teeth or surrounding tissues of childhood cancer survivors after CH. The literature search yielded a total of 15 identified non-randomized studies including at least 2315 patients (mean age at diagnosis or CH of 6.6 years; 36% male) followed for up to 22.9 years post CH.

Synthesis of available evidence indicated that CH was associated with increased risk for tooth agenesis by 147% (RR=2.47; Table 3). This translates clinically to every 7th child with CH having agenesis of at least one permanent tooth that would not develop otherwise (Table 4). This has been mostly attributed to intensive and repetitive CH at the time of initial hard-tissue formation [47].

Furthermore, CH was associated with additional developmental disturbances of the teeth including premature apexification, microdontia, enamel hypoplasia, arrested root development, and tooth discoloration – with the last three being most strongly associated with CH. Tooth discolorations and enamel hypoplasia could be attributed to CH agents like vincristine, vinblastine, and cyclophosphamide that might disturb ameloblast function, such as their microtubule calcium transport mechanism [42]. Microdontia or root malformations may be attributed to CH agents like vinblastine and vincristine that can interfere with the secretory function of mature odontoblasts / ameloblasts, which disrupts collagen fibril formation and dentin matrix secretion [12].

There are reports in the literature that dental developmental disturbances from CH are closely related to the patient's chronological or dental age—with younger patients being more severely affected [48-50]. In the present review the effect of patient age on dental adverse effects of CH could not be appropriately assessed through subgroup analysis or meta-regression, due to the limited material. Two identified studies providing different age subgroups indicated that potential differences existed between patients up to 5 years old and patients 6 years or older for tooth agenesis (RRs of 2.14 versus 0.67, respectively; 1 study), for microdontia (RRs of 10.70 versus 0.62, respectively; 1 study), and premature apexification (RRs of 8.50 versus 1.88, respectively; 1 study). On the other hand, age did not seem to have a big influence on arrested root development (RRs of 2.99 and 2.17; 2 studies) or tooth discoloration (RRs of 2.72 or 3.32; 1 study). However, these explorative findings could not be formally confirmed with robust evidence in the present review and caution is warranted by their interpretation.

The oral hygiene of CH patients was also significantly worse than controls, which was reflected in increased plaque accumulation and gingivitis (Table 3). However, this is not attributed directly to CH for example due to motoric disturbances of CH patients, but might be associated with specific phases of the antineoplastic treatment with low thrombocyte levels, where patients are instructed to refrain from toothbrushing to avoid bacteremia [51]. However, this suggested discontinuation of toothbrushing during thrombocytopenic and/or neutropenic phases is not shared by other researchers [52]. It is believed that thrombocytopenia should not be the sole determinant of oral hygiene procedures, as patients are able to perform oral hygiene procedures without bleeding at widely different levels of platelet counts [53]. However, in order to decrease the risk of any microtraumas due to toothbrushing, foam brushes and rinsing solutions can be recommended to perform oral hygiene during myeloablative chemotherapy instead of conventional toothbrushes [54]. In cases of preexisting mucosal irritation or thrombocytopenic hemorrhage, cotton swabs or sponges can be used instead of a toothbrush [55]. Other researchers suggest that throughout CH, the toothbrush should be placed in a 2% chlorhexidine solution which is replaced after each use in order to prevent bacterial contamination [56]. Another study indicated that the use of a fluoride gel led to significant improvement of the patients' caries experience throughout CH and could be a viable solution [35]. As no widely-accepted protocol for dental hygiene during CH exists at the time, future research on the effectiveness and adverse effects of various hygiene schemes might be prudent.

The average salivary flow rate among children treated with CH was significantly decreased compared to control patients (MD=-0.19 ml/min; Table 3). Hyposalivation has been reported in the literature as a direct consenquence of CH and has been observed even 5 years after CH [41].

Additionally, considerably greater caries experience was seen among CH patients than in controls in terms of higher DMFT index (MD=3.07 teeth; Table 3), which was attributed to significantly greater caries prevalence (DT; MD=3.55 teeth) and significantly less missing teeth (MT; MD=-0.56 teeth). The increased caries prevalence of CH patients might be explained by many factors. For one, CH-associated reduced salivary flow alters the microflora of the oral cavity, favoring caries-related bacteria [56]. Additionally, children on CH might require mouth moistening due to the existing hyposalivation / xerostomia, which is sometimes done by soft drinks that contain sugar [57]. However, other studies on children who received regular preventive protocols during CH found no differences in oral health parameters compared to controls

[58,59]. Generally, it is believed that the effect of CH on dental caries seems not to be a direct one, but rather an indirect consequence of poor oral hygiene and a lack of professional dental care during and after CH.

Finally, it must be noted that CH patients have been reported to have an increased burden of oral lesions compared to healthy patients, which sometimes develop into ulcers [34]. However, this could not be formally included in meta-analysis, due to the limited number of contributing studies and the nature of the measurements. Some evidence indicates that toothbrushing CH patients might have different progression of oral lesions than non-toothbrushing CH patients [34], while for both groups the presence of caries at the outset increased the probability of oral lesions during chemotherapy. Finally, the use of a novel hospital oral care protocol including toothbrushing has been shown to lead to a reduction in the prevalence of mucositis among CH patients [60], indicating potential gains of introducing such a systematic approach to the oral health of the pediatric cancer patiens.

Strengths and limitations

The strengths of this systematic review consist of the registration of its *a priori* protocol in PROSPERO [61] with transparent reporting of all post hoc actions [Appendix 7], its exhaustive literature search, its improved analytical methods [22], the use of the GRADE approach [28] to assess the quality of the meta-evidence, and open provision of the study dataset [26]. However, certain limitations also exist. First and foremost, this systematic review included only non-randomized trials that are at higher risk of bias than randomized ones [62]. As the scope of the review pertained more to adverse effects and diagnosis, non-randomized designs might be applicable [63], but all included studies were retrospective and therefore at higher risk of bias than prospective non-randomized studies [64]. Additionally, methodological issues existed for all included studies and these might have influenced the review's results. Finally, the limited number of included studies and their suboptimal reporting did not enable robust assessments of heterogeneity, as well as the conduct of several analyses for subgroup, small-study effects, and reporting biases that were planned a priori.

Clinical recommendations

Existing evidence from observational case-control studies indicates that chemotherapeutic medications in the treatment of childhood cancer is associated with disturbances of tooth development (tooth agenesis, tooth discoloration, arrested tooth development, enamel hypoplasia, microdontia, premature apexification), worse oral hygiene, oral lesions, hyposalivation, and increased caries experience compared to healthy children. Due to these detrimental effects on oral health, it is imperative that efforts are put forwards towards minimizing these adverse effects, so that cancer survivors have a better quality of life [65]. For example, it might be prude to do dental consultations on newly diagnosed children so that any pending preventive or therapeutic dental treatment can be concluded before the start of the antineoplastic therapy [52]. Some suggest that childhood cancer survivors are considered as a high-risk dental group and therefore need a close cooperation between the pediatric dentist and the pediatric oncologist. Consequently, a flexible cancer management scheme that also includes funds for preventive dentistry as well as hospital care pertaining to dental care and diet counseling [50,55] might be appropriate.

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FIGURES & LEGENDS

Fig. 1. PRISMA flow diagram for the identification and selection of eligible studies.

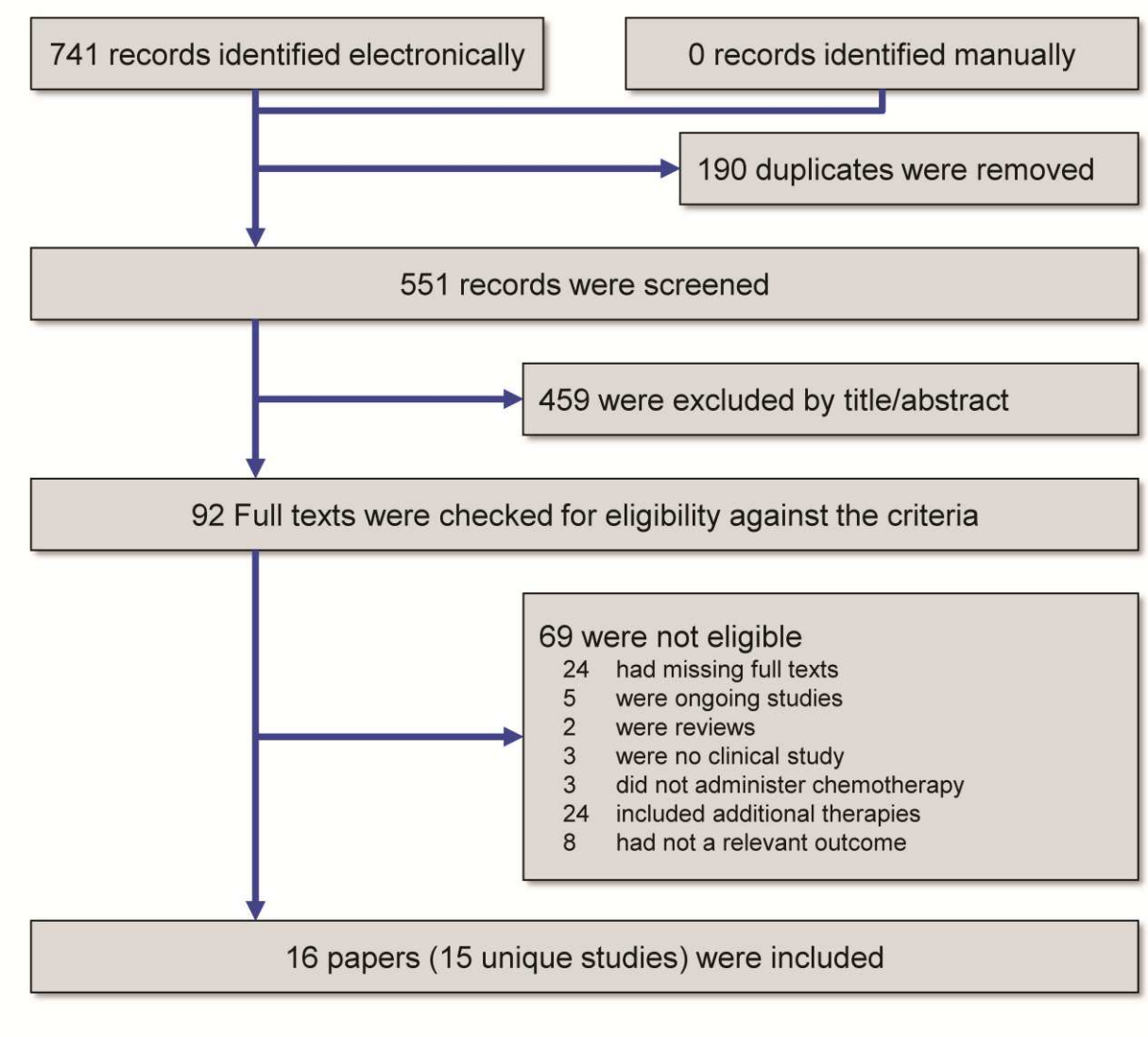

Fig. 2. Contour enhanced forest plot with random-effects meta-analysis on the prevalence of tooth agenesis among chemotherapy children and untreated children. CH, chemotherapy group; CI, confidence interval; CTR, control (non-chemotherapy) group; RR, relative risk.

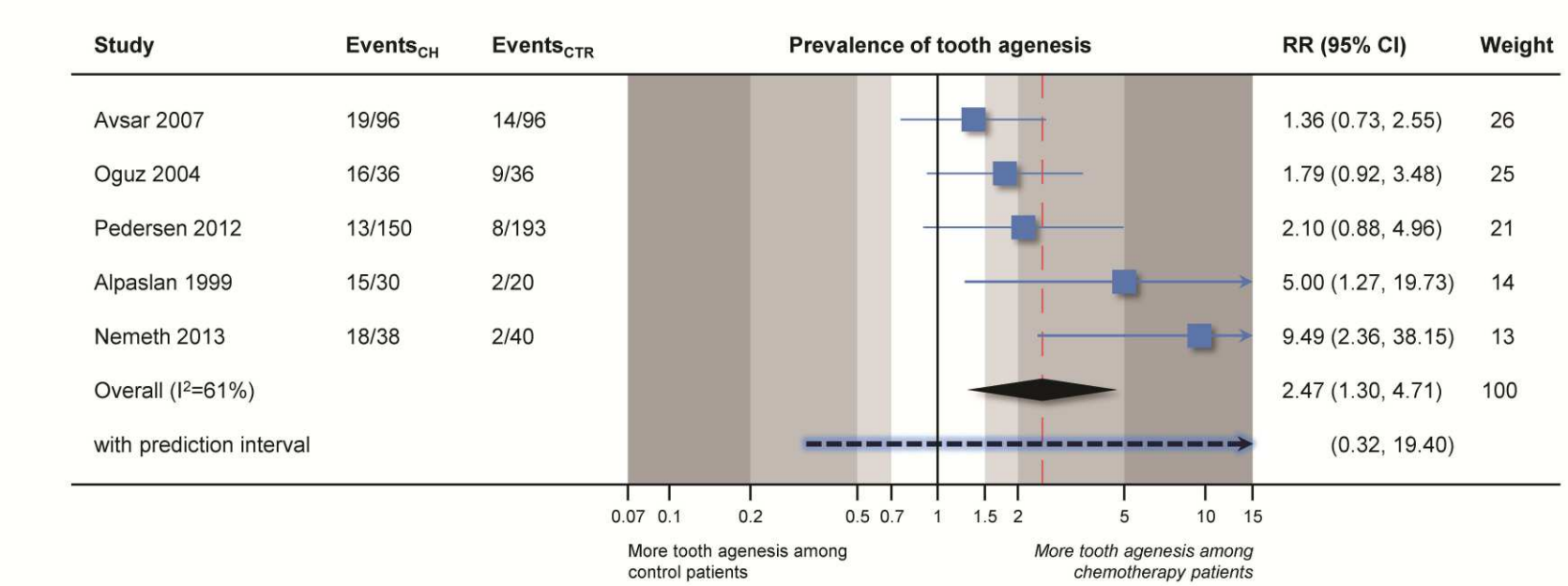

Fig. 3. Contour enhanced forest plot with random-effects meta-analysis on the prevalence of microdontia among chemotherapy children and untreated children. CH, chemotherapy group; CI, confidence interval; CTR, control (non-chemotherapy) group; RR, relative risk.

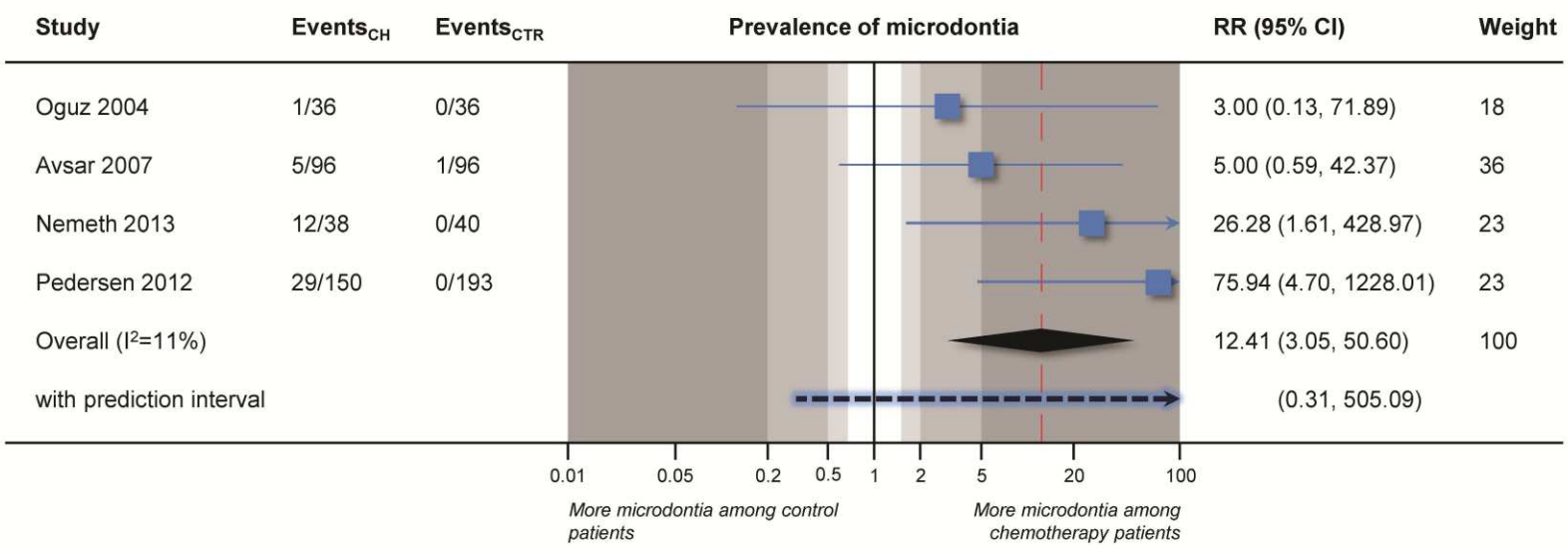

Fig. 4. Contour enhanced forest plot with random-effects meta-analysis on the prevalence of premature apexification among chemotherapy children and untreated children. CH, chemotherapy group; CI, confidence interval; CTR, control (non-chemotherapy) group; RR, relative risk.

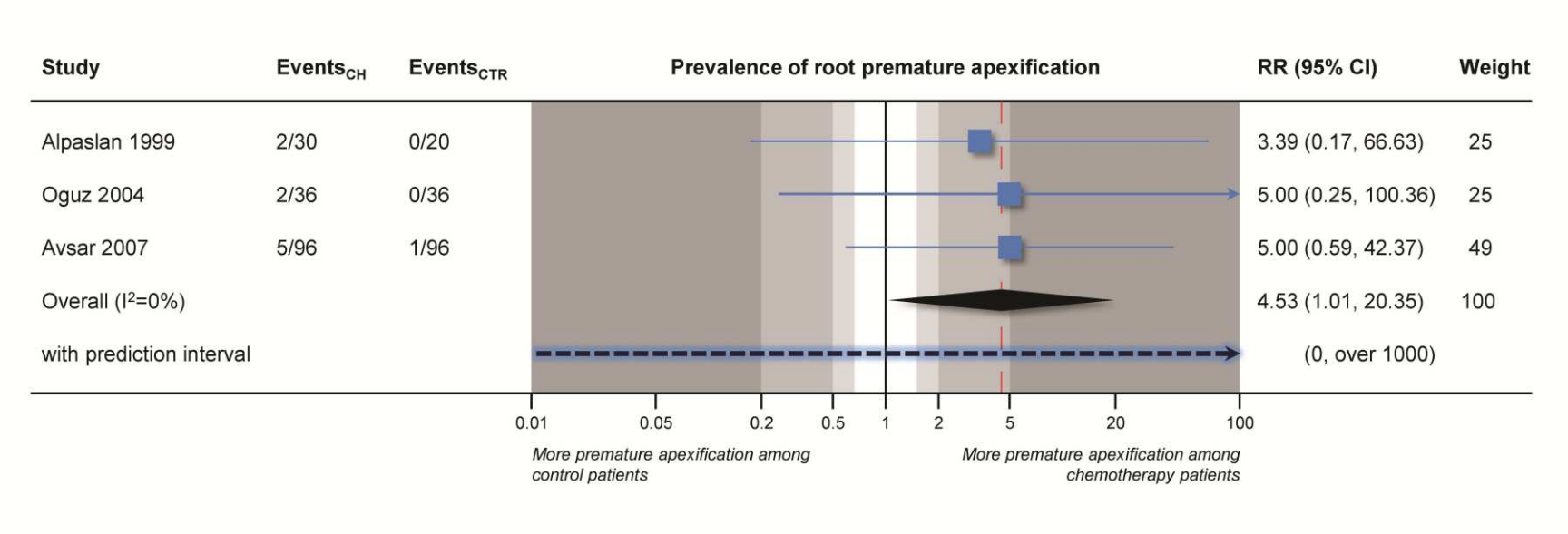

Table 1a
Characteristics of included studies.

Study ID	Design; setting; country*	Patients (M/F)	CH age† (yrs)	Evaluation age (yrs)	Follow-up (yrs)	Cancer type	CH type	Dental care
Alpaslan 1999 [33]	NRS; Uni; TR	CH: 30 (23/7) NC: 20 (15/5)	NR	CH: 10.2 NC: 10.3	1.4 post CH	HL, nHL	COPP, ABVD / BFM-90, LSA_2L_2	NR
Avşar 2007 [12]	NRS; Uni; TR	CH: 96 (48/48) NC: 96 (48/48)	6.4	CH: 10.8 NC: 10.5	2.5 post CH	Various	NR	No
Bonnaure-Mallet 1998 [34]	NRS; Uni; FR	CH: 131 (74/57)	6.6	NR	During CH	Various	NR	Prior/during CH
Cubukcu 2008$ [35]	NRS; Uni/Reg; TR	CH: 33 (21/12) NC: 34 (22/12)	NR	CH: 9.5 NC: 9.4	5.0 post CH	Various	Various	(Some) during CH
Dens 1995 [36]	NRS; Uni; BE	CH: 52 (NR) NC: 63 (NR)	NR	CH: (2.0-17.0) NC: *similar*	4.1 post CH	Various	NR	No
El –Housseiny 2007 [37]	NRS; Uni; EG	CH: 150 (82/68)	NR	CH: 7.0	NR	Various	Various	NR
Hutton 2010 [38]	NRS; Uni/Reg; GB	CH: 120 (69/51) NC: NR (*matched*)	(0-15.0)	CH/NC: (0-17.0)	4.3 post CH	Various	Anthracycline, alkylating, or platinum drugs	NR
Krasuska-Sawiska 2016 [39]	NRS; Hosp; PL	CH: 120 (NR) NC: 60 (NR)	7.5	CH: 11.5 NC: 12.2	2.5 post CH	Various	Various	Prior/during/after CH
Nemeth 2013 [40]; 2014 [41]	NRS; Uni/Sch; HU	CH: 38 (22/16) NC: 40 (18/22)	4.3	CH: 12.2 NC:12.5	6.9 post-CH	NR	Various	No
Oguz 2004 [42]	NRS; Uni; TR	CH: 36 (29/7) NC: 36 (*matched*)	7.1	CH: 10.0 NC: *matched*	2.6 post-CH	nHL	BFM-90; LSA_2L_2; LMT-89	NR
Ou-Yang 2010 [43]	NRS; Uni; TW	CH: 46 (NR) NC: 46 (*matched*)	7.5	CH: 7.5 NC: *matched*	During CH	ALL	Various	(Some) after CH
Pedersen 2012 [44]	NRS; Reg; DK	CH: 150 (NR) NC: 193 (NR)	(1.0-7.0)	CH/NC: (12.0-18.0)	NR	Various	Various	NR
Rosenberg 1987§ [45]	NRS; Hosp or Uni; US	CH: 17 (NR)	7.2	CH: ≥14.0	NR	ALL	L-2, L-10, or off-protocol	NR
Thomaz 2013 [13]	NRS; Uni/Sch; BR	CH: 20 (13/7) NC: 22 (NR)	NR	CH/NC: (3.0-15.0)	During CH	ALL	Ct (GBTLI-99), BFM-83	NR
Wilberg 2016 [46]	NRS; Uni; NO	CH: 111 (50/61) NC: 555 (263/292)	6.2	CH: 29.1 NC: 29.1	22.9 years post-CH	ALL	Norwegian / NSPHO protocol	(Some) after CH

* countries are given with their ISO Alpha-2 code.
† age pertains to diagnosis or treatment start and is given as mean (or in absence of mean as range in parenthesis).
$ some patients received also radiotherapy—those were excluded from the analyses.
§ compares treated patients with a historical sample of 10 other studies.

ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine protocol; ALL: Acute lymphoblastic leukemia; BFM: Berlin–Frankfurt–Münster-90 protocol; CH: chemotherapy (group); COPP: Cyclophosphamide, Oncovin, Procarbazine Hydrochloride, and Prednisone; HL: Hodgkin's lymphoma; Hosp: hospital clinic; M/F: male/female; mos: months; NC: no chemotherapy group; nHL: non-Hodgkin's lymphoma; NR: not reported; NRS: non-randomized study; NSPHO, Nordic Society of Pediatric Haematology and Oncology; Pat: patients; Reg: registry; Sch: school; Uni: university clinic; Hosp: Hospital; yrs: years.

Table 1b

Outcomes assessed by included studies.

Study ID	Outcomes
Alpaslan 1999 [33]	Eruption status; root malformations; premature apexification; agenesis, crown anomalies; soft tissue abnormalities; GI; PI; enamel defects and discolorations; hypoplasia; dmft/s; DMFT/S; cephalometric measurements
Avşar 2007 [12]	DMFT; GI; PI; Salivary flow rate; salivary buffer capacity; SM and LB counts; enamel disturbances (white/cream opacity, yellow/brown opacity, fine white lines, hypoplasia); dental development disturbances
Bonnaure-Mallet 1998 [34]	Frequency, severity and progress of oral lesions; caries at baseline
Cubukcu 2008 [35]	dmft/DMFT
Dens 1995 [36]	sIgA/IgG; Caries prevalence (DMFT/dmft); PI; SM/Lb counts
El –Housseiny 2007 [37]	Mucositis; fungal/viral/bacterial infected lesions; PI; GI; dmft/DMFT
Hutton 2010 [38]	dmft/DMFT; enamel opacities; Microdontia; dental trauma; dental trauma; gingival health
Krasuska-Sawiska 2016 [39]	PI; GI; dmft/DMFT; WSL; enamel defects (opacities, hypoplasia, combination); mucositis
Nemeth 2013 [40]; 2014 [41]	DMFT; salivary flow rate; salivary buffer capacity; bleeding and calculus; OHI-S; debris index; calculus index; agenesis; microdontia; macrodontia; unerrupted teeth; root malformation
Oguz 2004 [42]	PI; GI; dmft/s, DMFT/S; dmfs/DMFS; enamel discoloration; enamel defect; root malformations; unerupted teeth; agenesis; premature apexification; microdontia
Ou-Yang 2010 [43]	DEFTS/DMFT; SM and LB counts; salivary buffer capacity
Pedersen 2012 [44]	Microdontia; hypodontia
Rosenberg 1987 [45]	Root development (shortening, blunting of the apex, tapering/narrowing)
Thomaz 2013 [13]	Oral lesions; caries experience; PI; GI; deft/DMFT; sIgA
Wilberg 2016 [46]	Xerostomia; microdontia; enamel hypoplasia; hypodontia; DMFT; BOP; IDeI

BOP: bleeding on probing; deft: decayed, extracted, and filled deciduous tooth; DEFTS: edecayed, extracted, and filled permanent tooth surface; DMFT: Decayed Missing Filled Teeth for adult dentition (dmft for deciduous dentition); GI: gingival index; IDeI: individual defect index; LB: Lactobacillus; OHI-S: simplified oral health index; PI: plaque index; sIgA: salivary immunoglobin A; sIgG: salivary immunoglobin G; SM: Streptococcus mutans; WSL: White spot lesion.

Table 2
Methodological issues (with possible association to risk of bias) of included non-randomized studies with the Newcastle-Ottawa scale.

Study	Selection	Comparability	Exposure	Total stars
Alpaslan 1999 [33]	✪✪✪	✪✪	✪	6/9
Avşar 2007 [12]	✪✪✪	✪✪	✪	6/9
Bonnaure-Mallet 1998 [34]	✪✪		✪	3/9
Cubukcu 2008 [35]	✪✪✪✪	✪✪	✪	7/9
Dens 1995 [36]	✪✪	✪	✪	4/9
El –Housseiny 2007 [37]	✪✪		✪	3/9
Hutton 2010 [38]	✪✪✪	✪	✪	5/9
Krasuska-Sawiska 2016 [39]	✪✪	✪	✪	4/9
Nemeth 2013 [40]; 2014 [41]	✪✪✪	✪✪	✪✪	7/9
Oguz 2004 [42]	✪✪✪	✪✪	✪	6/9
Ou-Yang 2010 [43]	✪✪✪	✪✪	✪✪	7/9
Pedersen 2012 [44]	✪✪✪		✪✪	5/9
Rosenberg 1987 [45]	✪✪		✪	3/9
Thomaz 2013 [13]	✪✪✪✪		✪✪	6/9
Wilberg 2016 [46]	✪✪✪✪	✪✪	✪✪✪	9/9

Table 3

Results of performed meta-analyses.

Outcome	Studies (Patients)	Effect	95% CI	P	I^2 (95% CI)	tau^2 (95% CI)	95% prediction
Tooth agenesis	5 (735)	RR=2.47	1.30 to 4.71	0.006	61% (0% to 96%)	0.31 (0 to 5.03)	0.32 to 19.40
Enamel hypoplasia	2 (242)	RR=3.08	1.13 to 8.37	0.028	0% (0% to NC)	0 (0 to NC)	NC
Microdontia	4 (685)	RR=12.41	3.05 to 50.60	<0.001	11% (0% to 94%)	0.23 (0 to 28.81)	0.31 to 505.09
Arrested root development	2 (264)	RR=2.75	1.84 to 4.10	<0.001	0% (0% to 100%)	0 (0 to 31.72)	NC
Premature apexification	3 (314)	RR=4.53	1.01 to 20.35	0.049	0% (0% to NC)	0 (0 to NC)	0 to over 1000
Unerupted teeth	2 (122)	RR=1.43	0.40 to 5.15	0.583	69% (0% to 100%)	0.59 (0 to 873.45)	NC
Tooth discoloration	2 (122)	RR=3.25	1.89 to 5.61	<0.001	0% (0% to 99%)	0 (0 to 20.16)	NC
Plaque index	3 (444)	MD=0.60	0.32 to 0.89	<0.001	72% (1% to 99%)	0.05 (0 to 2.45)	-2.68 to 3.89
Gingival index	3 (444)	MD=0.38	0.16 to 0.61	0.001	57% (0% to 99%)	0.02 (0 to 1.66)	-2.00 to 2.77
DMFT[$]	3 (450)	MD=3.07	2.26 to 3.88	<0.001	0% (0% to 96%)	0 (0 to 13.55)	-2.17 to 8.32
DT	2 (258)	MD=3.55	2.71 to 4.39	<0.001	0% (0% to 100%)	0 (0 to 293.70)	NC
MT	2 (258)	MD=-0.56	-1.06 to -0.07	0.025	0% (0% to 99%)	0 (0 to 18.18)	NC
High salivary buffer capacity*	2 (170)	RR=1.03	0.26 to 4.07	0.969	93% (65% to NC)	0.92 (0.13 to NC)	NC
Salivary flow rate	2 (270)	MD=-0.19	-0.24 to -0.13	<0.001	0% (0% to 100%)	0 (0 to 5.08)	NC
High S. mutans counts*	2 (284)	RR=0.95	0.19 to 4.85	0.955	95% (75% to NC)	1.31 (0.21 to NC)	NC

CI: confidence interval; DMFT: decayed missing filled teeth; DT: decayed teeth; MD: mean difference; MT: missing teeth; NC: non-calculable; RR: relative risk.

* The 2 studies included in the meta-analysis are extremely heterogeneous (I^2>75%) and no single study can be robustly omitted; The results of the meta-analyses cannot be relied upon and current evidence indicates statistical noise in the absence of an existing effect.

[$] A single study [35] was omitted from the initial meta-analysis to alleviate extreme heterogeneity (initial meta-analysis: 4 studies; MD=2.25; 95% CI=0.65 to 3.86; P=0.006; I^2=83%)

Table 4
Numbers needed to treat for statistically significant meta-analyses of binary outcomes.

Outcome	**NNT**	**95% CI**
Tooth agenesis	7	3 to 30
Enamel hypoplasia	8	3 to 119
Microdontia	18	4 to 98
Arrested root development	4	2 to 7
Premature apexification	24	5 to 8334
Tooth discoloration	2	1 to 6

CI: confidence interval; NNT: number needed to treat.

Table 5a

Summary of Findings Table according to the GRADE approach (binary outcomes).

		Anticipated absolute effects[a] (95% CI)				
Outcome Studies (patients)	**Relative effects (95% CI)**	**CTR**	**CH**	**Difference**	**Quality of the evidence (GRADE)[c]**	**What happens**
Tooth agenesis 5 studies (735 patients)	RR 2.47 (1.30 to 4.71)	11.1%[b]	27.4% (14.4 to 52.3%)	16.3% more patients (3.3 to 41.2 more)	⊕○○○ very low[c,d] due to bias	May increase the risk of tooth agenesis
Enamel hypoplasia 2 studies (242 patients)	RR 3.08 (1.13 to 8.37)	6.5%[b]	20.0% (7.3 to 54.4%)	13.5% more patients (0.8 to 47.9 more)	⊕○○○ very low[c,d] due to bias	May increase the risk of enamel hypoplasia
Microdontia 4 studies (685 patients)	RR 12.41 (3.05 to 50.60)	0.5%[b]	6.2% (1.5 to 25.3%)	5.7% more patients (1.0 to 24.8 more)	⊕○○○ very low[c,d] due to bias	May increase the risk of microdontia
Arrested root development 2 studies (264 patients)	RR 2.75 (1.84 to 4.10)	18.6%[b]	51.2% (34.2 to 76.3%)	32.6% more patients (15.6 to 57.7 more)	⊕○○○ very low[c,d] due to bias	May increase the risk of root development arrest
Premature apexification 3 studies (314 patients)	RR 4.53 (1.01 to 20.35)	1.2%[b]	5.4% (1.2 to 24.4%)	4.2% more patients (0 to 23.2 more)	⊕○○○ very low[c,d] due to bias	May increase the risk of premature apexification
Unerupted teeth 2 studies (122 patients)	RR 1.43 (0.40 to 5.15)	22.2%[b]	31.7% (8.9 to 100%)	9.5% more patients (13.3 less to 92.1 more)	⊕○○○ very low[c,d] due to bias	No difference on tooth eruption
Tooth discoloration 2 studies (122 patients)	RR 3.25 (1.89 to 5.61)	22.2%[b]	72.2% (42 to 100%)	50.0% more patients (19.8 to 100.0 more)	⊕○○○ very low[c,d] due to bias	May increase the risk of tooth discoloration
High salivary buffer capacity 2 studies (270 patients)	RR 1.03 (0.26 to 4.07)	44.3%[b]	45.6% (11.5 to 100%)	1.3% more patients (32.8 less to 100 more)	⊕○○○ very low[c,d] due to bias	No difference on salivary buffer capacity
High S. mutans counts 2 studies (284 patients)	RR 0.95 (0.19 to 4.85)	38.9%[b]	37.0% (7.4 to 100%)	1.9% less patients (31.5 less to 100.0 more)	⊕○○○ very low[c,d] due to bias	No difference on high S. mutans counts

Dental effects of chemotherapy administered to children (binary outcomes).

Population & intervention: children receiving chemotherapy for any type of cancer.

Settings: university clinics (Denmark, Hungary, Taiwan, Turkey).

[a] The basis for the risk in the control group (e.g., the median control group risk across studies) is provided in footnotes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Reponse in the control group is based on random-effects meta-analytic pooling of the event rate from untreated patients of included studies.

[c] Starts from "low", due to the inclusion of non-randomized studies.

[d] Downgraded further by one point due to serious limitations (high risk of bias).

CH: chemo-therapy; CI: confidence interval; CTR: control group (no chemotherapy); GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 5b

Summary of Findings Table according to the GRADE approach (continuous outcomes).

		Anticipated absolute effects[a] (95% CI)				
Outcome Studies (patients)	**Relative effects (95% CI)**	**CTR**	**CH**	**Difference**	**Quality of the evidence (GRADE)[c]**	**What happens**
Plaque index 3 studies (444 patients)	-	0.82	-	0.60 higher score (0.32 to 0.89 higher)	⊕○○○ very low[c,d] due to bias	May increase the plaque index of patients
Gingival index 3 studies (444 patients)	-	0.72	-	0.38 higher score (0.16 to 0.61 higher)	⊕○○○ very low[c,d] due to bias	May increase the gingival index of patients
DMFT index 3 studies (450 patients)	-	3.84	-	3.07 higher score (2.26 to 3.88 higher)	⊕○○○ very low[c,d] due to bias	May increase the DMFT index of patients
DT index 2 studies (258 patients)	-	1.18	-	3.55 higher score (2.71 to 4.39 higher)	⊕○○○ very low[c,d] due to bias	May increase the DT index of patients
MT index 2 studies (258 patients)	-	2.25	-	0.56 lower score (0.07 to 1.06 lower)	⊕○○○ very low[c,d] due to bias	May decrease the MT index of patients
Salivary flow rate 2 studies (270 patients)	-	1.27	-	0.19 less ml/min (0.13 to 0.24 less)	⊕○○○ very low[c,d] due to bias	May decrease the salivary flow rate of patients

Dental effects of chemotherapy administered to children (continuous outcomes).
Population & intervention: children receiving chemotherapy for any type of cancer.
Settings: university clinics (Egypt, Hungary, Poland, Turkey).

[a] The basis for the risk in the control group (e.g., the median control group risk across studies) is provided in footnotes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Reponse in the control group is based on random-effects meta-analytic pooling of the event rate from untreated patients of included studies.

[c] Starts from "low", due to the inclusion of non-randomized studies.

[d] Downgraded further by one point due to serious limitations (high risk of bias).

CH, chemo-therapy; CI, confidence interval; CTR, control group (no chemotherapy); DMFT, decayed missing filled index; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Adverse effects of chemotherapy on the teeth of children with cancer: a systematic review with meta-analysis

Highlights

- Indications of dental adverse effects from chemotherapy for childhood cancer exist.
- This systematic review summarizes dental and oral adverse effects of chemotherapy.
- Chemotherapy is associated with increased risk of dental anomalies like agenesis.
- Chemotherapy is also associated with decreased salivary flow and increased caries.
- Comprehensive hospital dental care might be needed for childhood cancer survivors.

Adverse effects of chemotherapy on the teeth of children with cancer: a systematic review with meta-analysis

APPENDIX

Appendix 1. List of databases searched with search strategies, limitations, and hits (all searched on March 7, 2017).

Database	Pilot search	Filter	Hits
MEDLINE (via PubMed) https://www.ncbi.nlm.nih.gov/pubmed	chemotherapy AND (cancer OR oncol* OR survivor*) AND (child* OR pediatr* OR pedodon*) AND (tooth OR teeth OR dentition OR molar* OR incisor* OR canine* OR cuspid*)	Humans	318
Cochrane Database of Systematic Reviews http://www.cochranelibrary.com/	Same as PubMed		1
Cochrane Central Register of Controlled Trials http://www.cochranelibrary.com/	Same as PubMed		4
Cochrane Database of Abstracts of Reviews of Effects http://www.cochranelibrary.com/	Same as PubMed		0
Virtual Health Library* http://bvsalud.org/en/	Same as PubMed		12
Scopus https://www.scopus.com/	Same as PubMed	Human/Humans	264
Web of Science https://apps.webofknowledge.com/	Same as PubMed		113
ClinicalTrials.gov https://clinicaltrials.gov/	chemotherapy AND (cancer OR oncology OR survivor) AND (child OR children OR childhood OR pediatric OR pedodontic) AND (tooth OR teeth OR dentition OR molar OR incisor OR canine OR cuspid)		29
SUM (with duplicates)			741
SUM (without duplicates)			551

* covering among other the databases LILACS (Literatura Latino Americana em Ciências da Saúde), BBO (Brazilian Bibliography of Dentistry), WHOLIS (WHO Library Database), IBECS (Índice Bibliográfico Español en Ciencias de la Salud), CUMED (Cuba Medicina), PAHO (Pan American Health Organization), and MedCarib (Caribbean Health Sciences Literature).

Appendix 2. List of studies identified by the literature searches and their exclusion/inclusion status with reasons.

Nr.	Paper	Status
1	[No authors] Clinical guideline on dental management of pediatric patients receiving chemotherapy, hematopoietic cell transplantation, and/or radiation. Pediatric dentistry. 2004;26(7 Suppl):144-9.	Excluded by title
2	{NCT00002641} Surgery With or Without Chemotherapy in Treating Patients With Soft Tissue Sarcoma. [Completed]	Excluded by title
3	{NCT00002701} Combination Chemotherapy With or Without Bone Marrow Transplantation in Treating Patients With Acute Promyelocytic Leukemia. [Unknown status]	Excluded by title
4	{NCT00002764} Surgery With or Without Combination Chemotherapy in Treating Patients With Lung Metastases From Soft Tissue Sarcoma. [Completed]	Excluded by title
5	{NCT00002840} Radiation Therapy With and Without Combination Chemotherapy in Patients With Resected Anaplastic Oligodendroglioma. [Completed]	Excluded by title
6	{NCT00002895} Early Chemotherapy Based on CA 125 Level Alone Compared With Delayed Chemotherapy in Treating Patients With Recurrent Ovarian Epithelial , Fallopian Tube, or Primary Peritoneal Cancer. [Completed]	Excluded by title
7	{NCT00003636} Chemotherapy Plus Surgery in Treating Patients With Stage III or Stage IV Ovarian, Peritoneal, or Fallopian Tube Cancer. [Completed]	Excluded by title
8	{NCT00003643} Combination Chemotherapy in Treating Men With Germ Cell Cancer. [Unknown status].	Excluded by title
9	{NCT00005584} Combination Chemotherapy With or Without Radiation Therapy in Treating Patients With Hodgkin's Lymphoma. [Active, not recruiting]	Excluded by title
10	{NCT00014300} Glufosfamide in Treating Patients With Recurrent Glioblastoma Multiforme. [Completed]	Excluded by title
11	{NCT00017095} Biomarker (p53 Gene) Analysis and Combination Chemotherapy Followed by Radiation Therapy and Surgery in Treating Women With Large Operable or Locally Advanced or Inflammatory Breast Cancer. [Completed]	Excluded by title
12	{NCT00023842} BCG With or Without Mitomycin in Treating Patients With Bladder Cancer. [Completed]	Excluded by title
13	{NCT00041249} Brostallicin in Treating Patients With Locally Advanced or Metastatic Soft Tissue Sarcoma. [Completed]	Excluded by title
14	{NCT00042887} Chemotherapy With or Without Surgery in Treating Patients With Bladder Cancer. [Terminated]	Excluded by title
15	{NCT00053807} Interleukin-2, Interferon Alfa, and Fluorouracil Compared With Observation in Treating Patients Who Have Undergone Surgery for Kidney Cancer. [Completed]	Excluded by title
16	{NCT00085163} Celecoxib Combined With Fluorouracil and Leucovorin in Treating Patients With Resected Stage III Adenocarcinoma (Cancer) of the Colon. [Completed]	Excluded by title
17	{NCT00085735} Comparison of Radiation Therapy Regimens in Combination With Chemotherapy in Treating Young Patients With Newly Diagnosed Standard-Risk Medulloblastoma. [Completed]	Excluded by title
18	{NCT00096187} Pemetrexed Disodium in Treating Patients With Recurrent or Persistent Low-Risk Gestational Trophoblastic Tumor After a Molar Pregnancy. [Terminated]	Excluded by title
19	{NCT00227630} Pemetrexed Disodium and Cisplatin Followed By Surgery and Radiation Therapy in Treating Patients With Malignant Pleural Mesothelioma. [Completed]	Excluded by title
20	{NCT00392327} Chemotherapy and Radiation Therapy in Treating Young Patients With Newly Diagnosed, Previously Untreated, High-Risk Medulloblastoma. [Recruiting]	Excluded by title
21	{NCT01553071} Phase I Trial of IV Fenretinide (4-HPR) Plus IV Safingol for Patients With Relapsed Malignancies. [Recruiting]	Excluded by title
22	{NCT01898117} Triple-B Study;Carboplatin-cyclophosphamide Versus Paclitaxel With or Without Bevacizumab as First-line Treatment in Advanced Triple Negative Breast Cancer. [Recruiting]	Excluded by title
23	{NCT02276053} Study of Lacosamide as an Adjunctive Drug Treatment for Epilepsy in Patients With Brain Tumors. [Recruiting]	Excluded by title
24	{NCT02772094} Dendritic Cell-Based Tumor Vaccine Adjuvant Immunotherapy of Human Glioblastoma Multiforme (WHO Grade IV Gliomas). [Active, not recruiting]	Excluded by title
25	{NCT02892877} The French National Reference Centre of GTD. [Recruiting]	Excluded by title
26	Abdolkarimi B, Zareifar S, Mokhtari M. Face bones involvement and relapse in a case of childhood acute leukemia. Iranian Journal of Blood and Cancer. 2015;7(2):105-9.	Excluded by title
27	Ajibola A. Novel insights into the health importance of natural honey. Malaysian Journal of Medical Sciences. 2015;22(5):7-22.	Excluded by title
28	Alberth M, Torok J, Nemes J, Kiss C, Marton I. [Structural disorder of dental enamel caused by antineoplastic agents--case report]. Fogorvosi szemle. 2002;95(5):189-93.	Excluded by title
29	Amezcua CA, Bahador A, Naidu YM, Felix JC. Expression of human telomerase reverse transcriptase, the catalytic subunit of telomerase, is associated with the development of persistent disease in complete hydatidiform moles. American journal of obstetrics and gynecology. 2001;184(7):1441-6.	Excluded by title
30	Annibali S, Cristalli MP, Solidani M, Ciavarella D, La Monaca G, Suriano MM, et al. Langerhans cell histiocytosis: Oral/periodontal involvement in adult patients. Oral Diseases. 2009;15(8):596-601.	Excluded by title
31	Atas E, Kesik V. The False Positivity of Positron Emission Tomography Owing to Teething. Indian pediatrics. 2015;52(5):441.	Excluded by title
32	Barberia E, Hernandez C, Miralles V, Maroto M. Paediatric patients receiving oncology therapy: review of the literature and oral management guidelines. European journal of paediatric dentistry : official journal of European Academy of Paediatric Dentistry. 2008;9(4):188-94.	Excluded by title
33	Bardellini E, Amadori F, Majorana A. Oral hygiene grade and quality of life in children with chemotherapy-related oral mucositis: a randomized study on the impact of a fluoride toothpaste with salivary enzymes, essential oils, proteins and colostrum extract versus a fluoride toothpaste without menthol. International Journal of Dental Hygiene. 2016;14(4):314-9.	Excluded by title
34	Bascones-Martinez A, Munoz-Corcuera M, Gomez-Font R. [Oral secondary effects of radiotherapy and chemotherapy in cancer of the cervicofacial region]. Medicina clinica. 2013;141(2):77-81.	Excluded by title
35	Batschinski K, Dervisis NG, Kitchell BE. Evaluation of ifosfamide salvage therapy formetastatic canine osteosarcoma. Veterinary and Comparative Oncology. 2014;12(4):249-57.	Excluded by title
36	Benson RE, Rodd HD, North S, Loescher AR, Farthing PM, Payne M. Leukaemic infiltration of the mandible in a young girl. International journal of paediatric dentistry. 2007;17(2):145-50.	Excluded by title
37	Berkowitz RJ, Neuman P, Spalding P, Novak L, Strandjord S, Coccia PF. Developmental orofacial deficits associated with multimodal cancer therapy: case report. Pediatric dentistry. 1989;11(3):227-31.	Excluded by title
38	Beyazit Y, Kart T, Kuscu A, Arslan A, Kurt M, Aktas B, et al. Successful management of bleeding after dental procedures with application of blood stopper: a single center prospective trial. The journal of contemporary dental practice.	Excluded by title

	2011;12(5):379-84.	
39	Birkebaek NH, Helgestad JE. [Late endocrine and growth sequelae after cancer treatment in children]. Ugeskrift for laeger. 1994;156(32):4559-61, 64-5.	Excluded by title
40	Bisogno G, Soloni P, Conte M, Podda M, Ferrari A, Garaventa A, et al. Esthesioneuroblastoma in pediatric and adolescent age. A report from the TREP project in cooperation with the Italian Neuroblastoma and Soft Tissue Sarcoma Committees. BMC cancer. 2012;12.	Excluded by title
41	Bolze PA, Attia J, Massardier J, Seckl MJ, Massuger L, van Trommel N, et al. Formalised consensus of the European Organisation for Treatment of Trophoblastic Diseases on management of gestational trophoblastic diseases. European journal of cancer (Oxford, England : 1990). 2015;51(13):1725-31.	Excluded by title
42	Bonazzi C, Urso M, Dell'Anna T, Sacco S, Buda A, Cantu MG. Placental site trophoblastic tumor - An overview. Journal of Reproductive Medicine. 2004;49(8):585-8.	Excluded by title
43	Bonazzi C, Urso M, Dell'Anna T, Sacco S, Buda A, Cantu MG. Placental site trophoblastic tumor: an overview. The Journal of reproductive medicine. 2004;49(8):585-8.	Excluded by title
44	Brazao-Silva MT, Fernandes AV, Faria PR, Cardoso SV, Loyola AM. Ewing's sarcoma of the mandible in a young child. Brazilian dental journal. 2010;21(1):74-9.	Excluded by title
45	Brazão-Silva MT, Loyola AM, Cardoso SV, Fernandes AV, Faria PRd. Ewing's sarcoma of the mandible in a young child. Brazilian dental journal. 2010;21(1):74-9.	Excluded by title
46	Briefs L, Selbst SM. Pediatric emergency medicine. Pediatric Emergency Care. 2015;31(5):373-5.	Excluded by title
47	Brook I. Fusobacterial infections in children. Current Infectious Disease Reports. 2013;15(3):288-94.	Excluded by title
48	Burtner CR, Beard BC, Kennedy DR, Wohlfahrt ME, Adair JE, Trobridge GD, et al. Intravenous injection of a foamy virus vector to correct canine SCID-X1. Blood. 2014;123(23):3578-84.	Excluded by title
49	Butler J, Hooper KA, Petrie S, Lee R, Maurer-Stroh S, Reh L, et al. Estimating the fitness advantage conferred by permissive neuraminidase mutations in recent oseltamivir-resistant A(H1N1)pdm09 influenza viruses. PLoS pathogens. 2014;10(4):e1004065.	Excluded by title
50	Cabrerizo Merino MC, Onate Sanchez RE, Garcia Ballesta C, Ruiz Jimenez JI, De las Heras Gonzalez M. Dental anomalies caused by oncological treatment: case report. The Journal of clinical pediatric dentistry. 1998;22(3):261-4.	Excluded by title
51	Campana D, Coustan-Smith E, Manabe A, Kumagai M, Murti KG, Silvennoinen O, et al. Human B-cell progenitors and bone marrow microenvironment. Human cell. 1996;9(4):317-22.	Excluded by title
52	Captier G, Montoya P, Duche R, Le Barazer M, Bigorre M, Margueritte G. [Synovial sarcoma of the mandible in children. Apropos of a case]. Revue de stomatologie et de chirurgie maxillo-faciale. 1999;100(4):187-91.	Excluded by title
53	Carlsson G, Wahlin YB, Johansson A, Olsson A, Eriksson T, Claesson R, et al. Periodontal disease in patients from the original Kostmann family with severe congenital neutropenia. Journal of periodontology. 2006;77(4):744-51.	Excluded by title
54	Carol H, Fan MM, Harasym TO, Boehm I, Mayer LD, Houghton P, et al. Efficacy of CPX-351, (cytarabine:daunorubicin) liposome injection, against acute lymphoblastic leukemia (ALL) xenograft models of the Pediatric Preclinical Testing Program. Pediatric blood & cancer. 2015;62(1):65-71.	Excluded by title
55	Cetiner S, Alpaslan C. Long-term effects of cancer therapy on dental development: a case report. The Journal of clinical pediatric dentistry. 2004;28(4):351-3.	Excluded by title
56	Chen Y, Zheng XL, Fang DL, Yang Y, Zhang JK, Li HL, et al. Dual agent loaded PLGA nanoparticles enhanced antitumor activity in a multidrug-resistant breast tumor eenograft model. International journal of molecular sciences. 2014;15(2):2761-72.	Excluded by title
57	Cheng CF, Huang WH, Tsai TP, Ko EW, Liao YF. Effects of cancer therapy on dental and maxillofacial development in children: report of case. ASDC journal of dentistry for children. 2000;67(3):218-22, 161.	Excluded by title
58	Childs SK, Kozak KR, Friedmann AM, Yeap BY, Adams J, MacDonald SM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. International journal of radiation oncology, biology, physics. 2012;82(2):635-42.	Excluded by title
59	Cil T, Altintas A, Tamam Y, Battaloglu E, Isikdogan A. Low dose vincristine-induced severe polyneuropathy in a Hodgkin lymphoma patient: a case report (vincristine-induced severe polyneuropathy). Journal of pediatric hematology/oncology. 2009;31(10):787-9.	Excluded by title
60	Collins JJ, Geake J, Grier HE, Houck CS, Thaler HT, Weinstein HJ, et al. Patient-controlled analgesia for mucositis pain in children: A three- period crossover study comparing morphine and hydromorphone. J Pediatr 1996;129(5):722-8.	Excluded by title
61	Cortes-Ramírez J, Castelo O, Salazar L, Cortes R, Cortes J, Ayala C, et al. Oral alterations in children with cancer: literature review. J oral res (Impresa). 2014;3(4):262-8.	Excluded by title
62	da Fonseca MA, Murdoch-Kinch CA. Severe gingival recession and early loss of teeth in a child with chronic graft versus host disease: a case report. Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry. 2007;27(2):59-63.	Excluded by title
63	Dagi TF, Maccabe JJ. Metastatic trophoblastic disease presenting as a subarachnoid hemorrhage: report of two cases and review of the literature. Surgical neurology. 1980;14(3):175-84.	Excluded by title
64	Dahllof G, Jonsson A, Ulmner M, Huggare J. Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. 2001;120(5):459-65.	Excluded by title
65	Dahllof G, Rozell B, Forsberg CM, Borgstrom B. Histologic changes in dental morphology induced by high dose chemotherapy and total body irradiation. Oral surgery, oral medicine, and oral pathology. 1994;77(1):56-60.	Excluded by title
66	Dahllof G, Rozell B, Forsberg CM, Borgstrom B. Histologic-Changes in Dental Morphology Induced by High-Dose Chemotherapy and Total-Body Irradiation. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics. 1994;77(1):56-60.	Excluded by title
67	Daoud J, Toumi N, Bouaziz M, Ghorbel A, Jlidi R, Drira MM, et al. Nasopharyngeal carcinoma in childhood and adolescence: Analysis of a series of 32 patients treated with combined chemotherapy and radiotherapy. European Journal of Cancer. 2003;39(16):2349-54.	Excluded by title
68	David JM, Owens TA, Barwe SP, Rajasekaran AK. Gramicidin A induces metabolic dysfunction and energy depletion leading to cell death in renal cell carcinoma cells. Molecular cancer therapeutics. 2013;12(11):2296-307.	Excluded by title
69	Davido N, Rigolet A, Kerner S, Gruffaz F, Boucher Y. Case of Ewing's sarcoma misdiagnosed as a periapical lesion of maxillary incisor. Journal of endodontics. 2011;37(2):259-64.	Excluded by title
70	Davis LE, Hofmann NE, Li GH, Huang ET, Loriaux MM, Bracha S, et al. A case study of personalized therapy for osteosarcoma. Pediatric blood & cancer. 2013;60(8):1313-9.	Excluded by title

71	De Biase A, Ottolenghi L, Polimeni A, Benvenuto A, Lubrano R, Magliocca FM. Bilateral mandibular cysts associated with cyclosporine use: a case report. Pediatric nephrology (Berlin, Germany). 2001;16(12):993-5.	Excluded by title
72	de Gijt JP, van Capelle CI, Oosterhuis JW, van der Ploeg AT, van der Wal KG. Gingival overgrowth in Pompe disease: a case report. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons. 2011;69(8):2186-90.	Excluded by title
73	Demoor-Goldschmidt C, Minard-Colin V, Cassagneau E, Supiot S, Oberlin O, D'Hautuille C, et al. Ameloblastic fibrosarcoma of the mandible: Report of 2 chemosensitive pediatric cases. Journal of pediatric hematology/oncology. 2012;34(2):e72-e6.	Excluded by title
74	Dhayalan M, Anitha Jegadeeshwari L, Nagendra Gandhi N. Biological activity sources from traditionally usedtribe and herbal plants material. Asian Journal of Pharmaceutical and Clinical Research. 2015;8(6):11-23.	Excluded by title
75	Dickerhoff R, Lindner W, Scheiber W. Severe vincristine neurotoxicity in a patient with Charcot-Marie-Tooth disease. Pediatric hematology and oncology. 1988;5(1):61-4.	Excluded by title
76	Du L, Zhang X, Feng L, Chen J, Yang J, Liu H, et al. Treatment of nasopharyngeal carcinoma using simultaneous modulated accelerated radiation therapy via helical tomotherapy: A phase II study. Radiology and Oncology [Internet]. 2016; 50(2):[218-25 pp.].	Excluded by title
77	Du L, Zhang XX, Ma L, Feng LC, Li F, Zhou GX, et al. Clinical study of nasopharyngeal carcinoma treated by helical tomotherapy in China: 5-year outcomes. BioMed Research International. 2014;2014.	Excluded by title
78	Edner J, Rudd E, Zheng C, Dahlander A, Eksborg S, Schneider EM, et al. Severe bacteria-associated hemophagocytic lymphohistiocytosis in an extremely premature infant. Acta paediatrica (Oslo, Norway : 1992). 2007;96(11):1703-6.	Excluded by title
79	El-Faramawy N, El-Haddad K, Ali M, Talaat M. Impact of gamma radiation on the eruption rate of rat incisors. Radiation Effects and Defects in Solids. 2015;170(9):771-85.	Excluded by title
80	Elhaddaoui R, Bahije L, Chbicheb S, Zaoui F. Cervico-facial irradiation and orthodontic treatment. International Orthodontics. 2015;13(2):139-48.	Excluded by title
81	Erickson BP, Lee WW. Orbital cellulitis and subperiosteal abscess: A 5-year outcomes analysis. Orbit. 2015;34(3):115-20.	Excluded by title
82	Fallahian M. Familial gestational trophoblastic disease. Placenta. 2003;24(7):797-9.	Excluded by title
83	Fang P, Batra S, Hollander AB, Lin A, Hill-Kayser CE, Levin LM, et al. Development and evaluation of a standardized method and atlas for contouring primary and permanent dentition. Dentomaxillofacial Radiology. 2015;44(7).	Excluded by title
84	Feldman RJ, Maize JC. Multiple keratoacanthomas in a young woman: report of a case emphasizing medical management and a review of the spectrum of multiple keratoacanthomas. International journal of dermatology. 2007;46(1):77-9.	Excluded by title
85	Flavell DJ, Boehm DA, Okayama K, Kohler JA, Flavell SU. Therapy of human T-cell acute lymphoblastic leukaemia in severe combined immunodeficient mice with two different anti-CD7-saporin immunotoxins containing hindered or non-hindered disulphide cross-linkers. International journal of cancer. 1994;58(3):407-14.	Excluded by title
86	Forte V, Shimotakahara S, Crysdale WS, Thorner P. Recurring giant-cell granuloma at the site of previous radiation therapy. The Journal of otolaryngology. 1990;19(4):285-7.	Excluded by title
87	Freitas RDA, Barros SSLV, Quinderé LB. Oral Burkitt's lymphoma - Case report. Brazilian Journal of Otorhinolaryngology. 2008;74(3):458-61.	Excluded by title
88	Fromm M, Littman P, Raney RB, Nelson L, Handler S, Diamond G, et al. Late effects after treatment of twenty children with soft tissue sarcomas of the head and neck. Experience at a single institution with a review of the literature. Cancer. 1986;57(10):2070-6.	Excluded by title
89	Fukushima H, Kawanabe N, Murata S, Ishihara Y, Yanagita T, Balam TA, et al. SEA-4 is a Marker of Human Deciduous Periodontal Ligament Stem Cells. Journal of Dental Research. 2012;91(10):955-60.	Excluded by title
90	Fulda S, Honer M, Menke-Moellers I, Berthold F. Antiproliferative potential of cytostatic drugs on neuroblastoma cells in vitro. European journal of cancer (Oxford, England : 1990). 1995;31a(4):616-21.	Excluded by title
91	Gabris K, Orosz M, Suba Z. The effects on teeth of radiotherapy for nasal endodermal sinus tumor (yolk sac tumor) in childhood. International journal of oral and maxillofacial surgery. 2001;30(4):356-8.	Excluded by title
92	Gedik R, Çimen M. Multiple taurodontism: Report of case. Journal of Dentistry for Children. 2000;67(3):216-7.	Excluded by title
93	Giuliana G, Messina P. [Complications and prevention in radiotherapy and chemotherapy of malignant tumors of the cervical-facial region. II]. Stomatologia mediterranea : SM. 1986;6(4):529-40.	Excluded by title
94	Gocheva L. Late toxicity and cancerogenesis after large-field radiotherapy. Rentgenologiya i Radiologiya. 2008;47(4):260-5.	Excluded by title
95	Goho C. Chemoradiation therapy: effect on dental development. Pediatric dentistry. 1993;15(1):6-12.	Excluded by title
96	Gold JI, Kant AJ, Belmont KA, Butler LD. Practitioner review: Clinical applications of pediatric hypnosis. Journal of Child Psychology and Psychiatry and Allied Disciplines. 2007;48(8):744-54.	Excluded by title
97	Goldberg BE, Mongodin EF, Jones CE, Chung M, Fraser CM, Tate A, et al. The Oral Bacterial Communities of Children with Well-Controlled HIV Infection and without HIV Infection. PloS one. 2015;10(7):e0131615.	Excluded by title
98	Gomes MF, Kohlemann KR, Plens G, Silva MM, Pontes EM, da Rocha JC. Oral manifestations during chemotherapy for acute lymphoblastic leukemia: A case report. Quintessence International. 2005;36(4):307-13.	Excluded by title
99	Gomes MF, Martins LG, Alves MGO, De Morais Gouvêa Lima G, De Cássia Araújo Rocha R, Das Graças Vilela Goulart M. Interdisciplinary approach to the management of Ewing sarcoma: A case report. Special Care in Dentistry. 2012;32(6):265-9.	Excluded by title
100	Goodman ED, Fuks AB. The effects of anti-leukemic therapy on the developing dentition: case report. Pediatric dentistry. 1985;7(4):318-21.	Excluded by title
101	Goss AN. Bisphosphonates and orthodontics. Australian orthodontic journal. 2008;24(1):56-7.	Excluded by title
102	Govender D, Hadley GP. Recurrent Wilms' tumour or retroperitoneal teratoma? A challenging case. Virchows Archiv : an international journal of pathology. 1999;435(1):67-70.	Excluded by title
103	Graf WD, Chance PF, Lensch MW, Eng LJ, Lipe HP, Bird TD. Severe vincristine neuropathy in Charcot-Marie-Tooth disease type 1A. Cancer. 1996;77(7):1356-62.	Excluded by title
104	Gremmel T, Yanachkov IB, Yanachkova MI, Wright GE, Wider J, Undyala VV, et al. Synergistic Inhibition of Both P2Y1 and P2Y12 Adenosine Diphosphate Receptors As Novel Approach to Rapidly Attenuate Platelet-Mediated Thrombosis. Arteriosclerosis, thrombosis, and vascular biology. 2016;36(3):501-9.	Excluded by title
105	Grundy GE, Adkins KF, Savage NW. Cysts associated with deciduous molars following pulp therapy. Australian dental journal. 1984;29(4):249-56.	Excluded by title
106	Guida A, Meleti M, Vescovi P, Serpico R, Lucchese A, Lo Muzio L, et al. Anaplastic large cell anaplastic lymphoma kinase + non-Hodgkin lymphoma in a 10-year-old male discovered during dental visit: A case report. Head and Neck Oncology.	Excluded by title

	2012;4(5).	
107	Guijarro MV, Ghivizzani SC, Gibbs CP. Animal models in osteosarcoma. Frontiers in Oncology. 2014;4 JUL.	Excluded by title
108	Hafeman S, London C, Elmslie R, Dow S. Evaluation of liposomal clodronate for treatment of malignant histiocytosis in dogs. Cancer Immunology Immunotherapy. 2010;59(3):441-52.	Excluded by title
109	Haider A, Shaw JC. Treatment of acne vulgaris. Journal of the American Medical Association. 2004;292(6):726-35.	Excluded by title
110	Hakki SS, Aprikyan AA, Yildirim S, Aydinbelge M, Gokalp A, Ucar C, et al. Periodontal status in two siblings with severe congenital neutropenia: diagnosis and mutational analysis of the cases. Journal of periodontology. 2005;76(5):837-44.	Excluded by title
111	Hanazawa T, Kimura Y, Sakamaki H, Yamaguchi A, Nagumo M, Okano T. Burkitt's lymphoma involving the mandible: report of a case and review of Japanese cases. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 1998;85(2):216-20.	Excluded by title
112	Hantrakul S, Klangkaew N, Kunakornsawat S, Tansatit T, Poapolathep A, Kumagai S, et al. Clinical Pharmacokinetics and Effects of Vincristine Sulfate in Dogs with Transmissible Venereal Tumor (TVT). Journal of Veterinary Medical Science. 2014;76(12):1549-53.	Excluded by title
113	Hattab FN, Angmar-Mansson B. Oligodontia of the permanent dentition in two sisters with polycystic ovarian syndrome: case reports. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 1997;84(4):368-71.	Excluded by title
114	Hennewig U, Laws HJ, Eisert S, Gobel U. Bleeding and surgery in children with Glanzmann thrombasthenia with and without the use of recombinant factor VII a. Klinische Padiatrie. 2005;217(6):365-70.	Excluded by title
115	Henry CJ, McCaw DL, Brock KV, Stoker AM, Tyler JW, Tate DJ, et al. Association between cancer chemotherapy and canine distemper virus, canine parvovirus, and rabies virus antibody titers in tumor-bearing dogs. Journal of the American Veterinary Medical Association. 2001;219(9):1238-41.	Excluded by title
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482	Vespa N. [Controlled clinical study of tetranase in dentistry]. Minerva stomatologica. 1972;21(3):120-6.	Missing fulltext
483	Wellbury RR. Chemotherapy and childhood cancer: dental implications. Dental update. 1987;14(4):163-7.	Missing fulltext
484	{NCT00002462} RT or No RT Following Chemotherapy in Treating Patients With Stage III/IV Hodgkin's Disease. [Active, not recruiting]	Ongoing study
485	{NCT00006455} Combination Chemotherapy in Treating Children With Anaplastic Large Cell Lymphoma. [Unknown status]	Ongoing study
486	{NCT00049595} Comparison of Two Combination Chemotherapy Regimens in Treating Patients With Stage III or Stage IV Hodgkin's Lymphoma. [Active, not recruiting]	Ongoing study
487	{NCT00943423} PET Scan in Planning Treatment in Patients Undergoing Combination Chemotherapy For Stage IA or Stage IIA Hodgkin Lymphoma. [Active, not recruiting]	Ongoing study
488	{NCT02742363} Long Term Dental Effects in Adolescents Who Were Treated for Cancer in Childhood. [Recruiting]	Ongoing study

489	de Morais EF, Lira JAS, Macedo RAP, dos Santos KS, Elias CTV, Morais MLSA. Oral manifestations resulting from chemotherapy in children with acute lymphoblastic leukemia. Brazilian Journal of Otorhinolaryngology. 2014;80(1):78-85.	Review
490	Effinger KE, Migliorati CA, Hudson MM, McMullen KP, Kaste SC, Ruble K, et al. Oral and dental late effects in survivors of childhood cancer: A Children's Oncology Group report. Supportive Care in Cancer. 2014;22(7):2009-19.	Review
491	Ataç AS. Oral and dental care in acute lymphoblastic leukemia: Role of pediatric dentist. UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi. 2009;19(1):58-62.	No clinical study
492	Dotto CA, Antoniazzi JH. Opinion makers: odontopediatria. 2002:147-.	No clinical study
493	Nawrocki L, Libersa P, Lambilliotte A, Pichon F, Turck D, Lafforgue P, et al. Side effects of chemotherapy on dental development. Archives de Pediatrie. 2001;8(7):754-6.	No clinical study
494	Basu P. News feature: Double jeopardy. Nature Medicine. 2005;11(11):1132-3.	No chemotherapy
495	Marec-Berard P, Azzi D, Chaux-Bodard AG, Lagrange H, Gourmet R, Bergeron C. Long-term effects of chemotherapy on dental status in children treated for nephroblastoma. Pediatric hematology and oncology. 2005;22(7):581-8.	No chemotherapy
496	Singh N, Bakhshi S. Imatinib-induced dental hyperpigmentation in childhood chronic myeloid leukemia. Journal of pediatric hematology/oncology. 2007;29(3):208-9.	No chemotherapy
497	Alberth M, Kovalecz G, Nemes J, Math J, Kiss C, Marton IJ. Oral health of long-term childhood cancer survivors. Pediatric blood & cancer. 2004;43(1):88-90.	Additional treatments used
498	Cho SY, Cheng AC, Cheng MCK. Oral care for children with leukaemia. Hong Kong Medical Journal. 2000;6(2):203-8.	Additional treatments used
499	Cubukcu CE, Sevinir B. Dental health indices of long-term childhood cancer survivors who had oral supervision during treatment: a case-control study. Pediatric hematology and oncology. 2008;25(7):638-46.	Additional treatments used
500	Demasi OF, Fava M, Carrillo CM, Amaral TGdFS, Odone Filho V. Tooth abnormalities in pediatric patients submitted to antineoplastic treatment for central nervous system neoplasms. Braz dent sci. 2016;19(3):39-46.	Additional treatments used
501	Doğan C, Haytaç C, Antmen B, Şaşmaz I, Tanyeli A. Oral health status in children with acute lymphoblastic leukemia and lymphoma. Turkish Journal of Haematology. 2001;18(3):179-83.	Additional treatments used
502	Duggal MS, Curzon MEJ, Bailey CC, Lewis IJ, Prendergast M. Dental parameters in the long term survivors of childhood cancer compared with siblings. Oral oncology. 1997;33(5):348-53.	Additional treatments used
503	Gera R, Saah EN, Scott-Emuakpor AB, Kulkarni R. Disabilities in adolescents with cancer. International Journal on Disability and Human Development. 2008;7(3):245-51.	Additional treatments used
504	Goncalves CF, Silva M, Costa LR, de Toledo OA. One-year follow-up of Atraumatic Restorative Treatment(ART) for dental caries in children undergoing oncohematological treatment: a pragmatic trial. Bmc Oral Health. 2015;15.	Additional treatments used
505	Hong CH, daFonseca M. Considerations in the pediatric population with cancer. Dental clinics of North America. 2008;52(1):155-81, ix.	Additional treatments used
506	Hsieh SG, Hibbert S, Shaw P, Ahern V, Arora M. Association of cyclophosphamide use with dental developmental defects and salivary gland dysfunction in recipients of childhood antineoplastic therapy. Cancer. 2011;117(10):2219-27.	Additional treatments used
507	Javed F, Utreja A, Bello Correa FO, Al-Askar M, Hudieb M, Qayyum F, et al. Oral health status in children with acute lymphoblastic leukemia. Critical Reviews in Oncology/Hematology. 2012;83(3):303-9.	Additional treatments used
508	Joshi S, Hegde AM, Rai K, Shetty S. Evaluation of salivary sialic acid levels in acute lymphoblastic leukemic children and its correlation with dental caries experience. The Journal of clinical pediatric dentistry. 2013;37(3):309-13.	Additional treatments used
509	Kaste SC, Hopkins KP, Bowman LC, Santana VM. Dental abnormalities in children treated for neuroblastoma. Medical and pediatric oncology. 1998;30(1):22-7.	Additional treatments used
510	Lauritano D, Petruzzi M. Decayed, missing and filled teeth index and dental anomalies in long-term survivors leukaemic children: A prospective controlled study. Medicina Oral Patologia Oral Y Cirugia Bucal. 2012;17(6):E977-E80.	Additional treatments used
511	Marec-Berard P, Bergeron C, Frappaz D, Philip T, Gorry F, Chaux-Bodard AG, et al. Anomalies of dental development in children treated by chemotherapy. Archives De Pediatrie. 2002;9(11):1212-3.	Additional treatments used
512	Otmani N, Khattab M. Oral Burkitt's lymphoma in children: the Moroccan experience. International journal of oral and maxillofacial surgery. 2008;37(1):36-40.	Additional treatments used
513	Paparella ML, Olvi LG, Brandizzi D, Keszler A, Santini-Araujo E, Cabrini RL. Osteosarcoma of the jaw: An analysis of a series of 74 cases. Histopathology. 2013;63(4):551-7.	Additional treatments used
514	Pels E, Mielnik-Błaszczak M. Oral hygiene in children suffering from acute lymphoblastic leukemia living in rural and urban regions. Annals of Agricultural and Environmental Medicine. 2012;19(3):529-33.	Additional treatments used
515	Proc P, Szczepańska J, Skiba A, Zubowska M, Fendler W, Młynarski W. Dental anomalies as late adverse effect among young children treated for cancer. Cancer Research and Treatment. 2016;48(2):658-67.	Additional treatments used
516	Sariban E, Donahue A, Magrath IT. Jaw involvement in American Burkitt's Lymphoma. Cancer. 1984;53(8):1777-82.	Additional treatments used
517	Signorelli C, McLoone JK, Wakefield CE, Cohn RJ. Dental hygiene in childhood cancer survivors: The importance of tertiary long term follow-up care. Pediatric Blood and Cancer. 2015;62(5):921.	Additional treatments used
518	Skinner R. Long-term effects of cancer therapy in children - organs, systems and tissues. Paediatrics and Child Health. 2012;22(5):201-6.	Additional treatments used
519	Uderzo C, Fraschini D, Balduzzi A, Galimberti S, Arrigo C, Biagi E, et al. Long-term effects of bone marrow transplantation on dental status in children with leukaemia. Bone marrow transplantation. 1997;20(10):865-9.	Additional treatments used
520	Valéra MC, Noirrit-Esclassan E, Pasquet M, Vaysse F. Oral complications and dental care in children with acute lymphoblastic leukaemia. Journal of Oral Pathology and Medicine. 2015;44(7):483-9.	Additional treatments used
521	Craig JV, Gibson F, Glenny AM. Audit to monitor the uptake of national mouth care guidelines for children and young people being treated for cancer. Supportive Care in Cancer. 2011;19(9):1335-41.	No relevant outcome
522	Dahllof G, Nasman M, Borgstrom A, Modeer T, Forsberg CM, Heimdahl A, et al. Effect of chemotherapy on dental maturity in children with hematological malignancies. Pediatric dentistry. 1989;11(4):303-6.	No relevant outcome
523	de Oliveira Lula EC, de Oliveira Lula CE, Alves CM, Lopes FF, Pereira AL. Chemotherapy-induced oral complications in leukemic patients. International journal of pediatric otorhinolaryngology. 2007;71(11):1681-5.	No relevant outcome
524	Farsi DJ. Children Undergoing Chemotherapy: Is It Too Late for Dental Rehabilitation? The Journal of clinical pediatric dentistry. 2016;40(6):503-5.	No relevant outcome
525	Fayle SA, Curzon ME. Oral complications in pediatric oncology patients. Pediatric dentistry. 1991;13(5):289-95.	No relevant outcome
526	Sixou JL, Aubry-Leuliette A, De Medeiros-Battista O, Lejeune S, Jolivet-Gougeon A, Solhi-Pinsard H, et al. Capnocytophaga in the dental plaque of immunocompromised children with cancer. International journal of paediatric	No relevant outcome

	dentistry. 2006;16(2):75-80.	
527	Sixou JL, De Medeiros-Batista O, Gandemer V, Bonnaure-Mallet M. The effect of chemotherapy on the supragingival plaque of pediatric cancer patients. Oral oncology. 1998;34(6):476-83.	No relevant outcome
528	Wallace WHB, Thompson L, Anderson RA. Long term follow-up of survivors of childhood cancer: Summary of updated SIGN guidance. BMJ (Online). 2013;346(7901).	No relevant outcome
529	Alpaslan G, Alpaslan C, Gogen H, Oguz A, Cetiner S, Karadeniz C. Disturbances in oral and dental structures in patients with pediatric lymphoma after chemotherapy: a preliminary report. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 1999;87(3):317-21.	Included
530	Avsar A, Elli M, Darka O, Pinarli G. Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 2007;104(6):781-9.	Included
531	Bonnaure-Mallet M, Bunetel L, Tricot-Doleux S, Guerin J, Bergeron C, LeGall E. Oral complications during treatment of malignant diseases in childhood: effects of tooth brushing. European journal of cancer (Oxford, England : 1990). 1998;34(10):1588-91.	Included
532	Cubukcu CE, Gunes AM. Caries experience of leukemic children during intensive course of chemotherapy. The Journal of clinical pediatric dentistry. 2008;32(2):155-8.	Included
533	Dens F, Boute P, Vinckier F, Declerck D. Quantitative determination of immunologic components of salivary gland secretion in long-term, event-free pediatric oncology patients. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and. 1995;79(6):701-4.	Included
534	El -Housseiny AA, Saleh SM, El-Masry AA, Allam AA. Assessment of oral complications in children receiving chemotherapy. Journal of Clinical Pediatric Dentistry. 2007;31(4):267-73.	Included
535	Hutton A, Bradwell M, English M, Chapple I. The oral health needs of children after treatment for a solid tumour or lymphoma. International journal of paediatric dentistry. 2010;20(1):15-23.	Included
536	Krasuska-Sawiska E, Broyna A, Dembowska-Bagiska B, Olczak-Kowalczyk D. Factors influencing caries incidence in permanent teeth in children/ adolescents under and after anti-neoplastic treatment. Wspolczesna Onkologia. 2016;20(1):45-51.	Included
537	Nemeth O, Hermann P, Kivovics P, Garami M. Long-term effects of chemotherapy on dental status of children cancer survivors. Pediatric hematology and oncology. 2013;30(3):208-15.	Included
538	Nemeth O, Kivovics M, Pinke I, Marton K, Kivovics P, Garami M. Late effects of multiagent chemotherapy on salivary secretion in children cancer survivors. Journal of the American College of Nutrition. 2014;33(3):186-91.	Included
539	Oguz A, Cetiner S, Karadeniz C, Alpaslan G, Alpaslan C, Pinarli G. Long-term effects of chemotherapy on orodental structures in children with non-Hodgkin's lymphoma. European journal of oral sciences. 2004;112(1):8-11.	Included
540	Ou-Yang LW, Chang PC, Tsai AI, Jaing TH, Lin SY. Salivary microbial counts and buffer capacity in children with acute lymphoblastic leukemia. Pediatric dentistry. 2010;32(3):218-22.	Included
541	Pedersen LB, Clausen N, Schroder H, Schmidt M, Poulsen S. Microdontia and hypodontia of premolars and permanent molars in childhood cancer survivors after chemotherapy. International journal of paediatric dentistry. 2012;22(4):239-43.	Included
542	Rosenberg SW, Kolodney H, Wong GY, Murphy ML. Altered dental root development in long-term survivors of pediatric acute lymphoblastic leukemia. A review of 17 cases. Cancer. 1987;59(9):1640-8.	Included
543	Thomaz EBAF, Mouchrek JCE, Silva AQ, Guerra RNM, Libério SA, da Cruz MCFN, et al. Longitudinal assessment of immunological and oral clinical conditions in patients undergoing anticancer treatment for leukemia. International journal of pediatric otorhinolaryngology. 2013;77(7):1088-93.	Included
544	Wilberg P, Kanellopoulos A, Ruud E, Hjermstad MJ, Fossa SD, Herlofson BB. Dental abnormalities after chemotherapy in long-term survivors of childhood acute lymphoblastic leukemia 7-40 years after diagnosis. Supportive Care in Cancer 2016;24(4):1497-506.	Included

Appendix 3. Assessment of the methodological adequacy (potentially associated with risk of bias) of included studies with a modified Newcastle-Ottawa tool for cohort studies.

	Alpaslan 1999	Avsar 2007	Bonnaure-Mallet 1998	Cubukcu 2009	Dens 1995	El-Housseiny 2007	Hutton 2010	Krasuska-Sawiska 2016	Nemeth 2013; 2014	Oguz 2004	Ou-Yang 2010	Pedersen 2012	Rosenberg 1987	Thomaz 2013	Wilberg 2015
Selection															
Is the case definition adequate?	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪
Representativeness of the cases	✪	✪	✪	✪		✪	✪			✪		✪	✪	✪	✪
Selection of Controls			NA	✪		NA	✪		✪		✪		NA	✪	✪
Definition of Controls	✪	✪	NA	✪	✪	NA		✪	✪	✪	✪	✪	NA	✪	✪
Comparability															
Comparability of cases and controls on the basis of the design or analysis	✪✪	✪✪	NA	✪✪	✪	NA	✪	✪	✪✪	✪✪	✪✪		NA		✪✪
Exposure															
Ascertainment of exposure	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪	✪
Same method of ascertainment for cases and controls*			NA			NA			✪		✪	✪	NA	✪	✪
Non-Response Rate			NA			NA							NA		✪

NA: not applicable

* Star was given only when a study explicitly stated that the patient in the control group were unexposed.

Appendix 4. Re-analysis with univariable/multivariable linear regression of DMFT data from the Cubukcu et al., 2008 study.

		Univariable				**Multivariable**		
Factor	**Category**	**Coefficient**	**95% CI**	**P**		**Coefficient**	**95% CI**	**P**
Chemotherapy	Yes	0.02	-1.16,1.21	0.97		0.01	-1.14,1.16	0.99
	No	Reference				Reference		
Gender	Male	-0.69	-1.92,0.53	0.26		Not added	-	-
	Female	Reference				Reference		
Age at diagnosis group	6 years or older	1.49	0.25,2.73	0.02		1.49	0.23,2.74	0.02
	Up to 5 years	Reference				Reference		

CI: confidence interval.

Appendix 5. Random-effects meta-regression analyses of tooth agenesis with modifying factors.

Outcome	Studies	RR	95% CI	P
Patient age (per year)	3	0.54	0.01 to 45.09	0.33
Patient sex (per % male patients in the sample)	4	0.99	0.85 to 1.17	0.90
Follow-up (per year)	4	1.30	0.50 to 3.39	0.36

CI: confidence interval; RR, relative risk.

Appendix 6. Sensitivity analyses between large and non-large studies (judged arbitrarily with a cut-off of 100 patients/study).

	Large				Non-large			
Outcome	**Studies**	**Effect**	**95% CI**		**Studies**	**Effect**	**95% CI**	**P (large vs non-large)**
Tooth agenesis	2	RR=1.58	0.95 to 2.63		3	RR=3.71	1.38 to 9.94	0.39
Enamel hypoplasia	1	RR=3.00	0.32 to 28.62		1	RR=3.10	1.01 to 9.46	NC
Microdontia	2	RR=16.74	1.18 to 236.64		2	RR=10.19	1.24 to 83.92	0.88
Arrested root development	1	RR=2.94	1.84 to 4.71		1	RR=2.29	1.07 to 4.93	NC
Premature apexification	1	RR=5.00	0.59 to 42.37		2	RR=4.11	0.50 to 34.03	0.61
Unerupted teeth	0	-	-		2	RR=1.43	0.40 to 5.15	-
Tooth discoloration	0	-	-		2	RR=3.25	1.89 to 5.61	-
Plaque index	2	MD=0.61	0.12 to 1.10		1	MD=0.59	0.32 to 0.86	0.93
Gingival index	2	MD=0.46	0.16 to 0.76		1	MD=0.24	-0.01 to 0.49	0.60
DMFT	2	MD=3.45	2.44 to 4.46		1	MD=2.40	1.05 to 3.75	0.13
DT	1	MD=3.89	2.75 to 5.03		1	MD=3.13	1.88 to 4.38	NC
MT	1	MD=-0.41	-1.53 to 0.71		1	MD=-0.60	-1.15 to -0.05	NC
High salivary buffer capacity	0	-	-			RR=1.03	0.26 to 4.07	-
Salivary flow rate	1	MD=-0.18	-0.24 to -0.12		1	MD=-0.28	-0.50 to -0.06	NC
High S. mutans counts	1	RR=2.18	1.34 to 3.56		1	RR=0.41	0.24 to 0.70	NC

CI: confidence interval; DMFT: decayed missing filled teeth; DT: decayed teeth; MD: mean difference; MT: missing teeth; NC: non-calculable; RR: relative risk.

Appendix 7. Additional review details

Contributors

DMB, SNP and TE conceived the study. DMB wrote the first draft of the protocol and all authors revised the protocol. DMB and SNP did study selection, data extraction, and methodological assessment, while GR and TE resolved conflicts. SNP performed the analysis and DMB wrote the first draft of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content and approved the final version. SNP is the guarantor.

Deviations from the initial protocol

- The primary outcome of the review was changed from caries experience to tooth agenesis. This was done as caries experience might correspond to cavitated/non-cavitated lesions of variable size that might be treated with a simple filling—whereas tooth agenesis results in obvious tooth loss and therefore greater burden and treatment costs. Tooth agenesis was already included in the initial protocol, but as a secondary outcome.
- We also decided to adjust the list of secondary outcomes to all outcomes that were identified and included in meta-analyses. These are however listed as secondary outcomes in the paper and are given lower priority.
- Additional subgroup/meta-regression analyses were planned in the review protocol, but could not be conducted as only one meta-analysis included more than 5 studies and limited data was available.
- Sensitivity analyses planned a priori between randomized and non-randomized studies could not be conducted as no randomized trials existed. Likewise, sensitivity analysis on methodological grounds between prospective and retrospective non-randomized studies could not be conducted, as only retrospective studies were identified.
- Indications of reporting biases (including small-study effects and publication bias) were planned to be conducted for meta-analyses of ≥ 10 studies (Sterne et al., 2011) using contour-enhanced funnel plots and Egger's test (Egger et al., 1997). However, all meta-analyses included less than 10 studies and such analyses were not possible.